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Health and Environmental Effects Profile for Epichlorohydrin

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16. ABSTRACT

The Health and Environmental Effects Profile for epichlorohydrin was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Epichlorohydrin has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for epichlorohydrin is 9.9×10^{-3} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for epichlorohydrin is 100.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR EPICHLOROHYDRIN

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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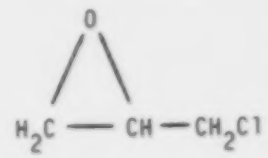
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BODT	Biochemical oxygen demand, theoretical
CAS	Chemical Abstract Service
CHO	Chinese hamster ovary
CNS	Central nervous system
COD	Chemical oxygen demand
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Median effect concentration
i.m.	Intramuscular
i.p.	Intraperitoneal
K_{oc}	Soil/Water partition coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
SMR	Standardarized mortality ratio
STEL	Short-term exposure level
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Epichlorohydrin is the common name for 1-chloro-2,3-epoxypropane. Synonyms include the following: 3-chloro-1,2-epoxypropane; (chloromethyl)-ethylene oxide; 2-(chloromethyl)oxirane; chloropropylene oxide; γ-chloropropylene oxide; 3-chloropropene 1,2-oxide; 2-chloromethyl oxirane; glycidyl chloride; 3-chloro-1,2-propylene oxide; α-epichlorohydrin; ECH; ECHH; SKEKhG; 1,2-epoxy-3-chloropropane; 2,3-epoxypropylchloride; and glycerol epichlorohydrine. The structure, molecular weight and molecular formula for epichlorohydrin are as follows:



Molecular weight: 92.53

Molecular formula: C_3H_5OCl

The CAS Registry number is 106-89-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

At ambient temperature, epichlorohydrin is a clear liquid that is volatile and flammable (Weast, 1978). Selected physical properties are listed below:

Melting point:	-25.6°C	Windholz (1983)
Boiling point (760 mmHg):	117.9°C	Windholz (1983)
Density:	1.1812 (d_4^{20})	Windholz (1983)
Vapor pressure (in mmHg):		
at 16.6°C	10	Sax (1975)
at 30°C	22	Verschueren (1977)
Flashpoint (open cup):	40°C	Windholz (1983)

Water solubility:		
at 10°C	6.52%	U.S. EPA (1984a)
at 20°C	6.58%	U.S. EPA (1984a)
Odor threshold in water:	3 ppm	Amoore and Hautala (1983)
Odor threshold in air:	10 ppm	Hine et al. (1981)
	0.93 ppm	Amoore and Hautala (1983)
Heat of combustion:	4524.4 cal/g	U.S. EPA (1984a)
Liquid viscosity (25°C):	0.0103 poises	U.S. EPA (1984a)
Refractive index (25°C):	n_D 1.4358	U.S. EPA (1984a)
Heat capacity:		
25°C	31.5 cal/mol°C	U.S. EPA (1984a)
100°C	40.0 cal/mol°C	U.S. EPA (1984a)
Heat of formation (25°C):	-35.6 kcal/mol	U.S. EPA (1984a)
Explosive limits:		
volume % in air	3.8-21.0	U.S. EPA (1984a)
Heat of fusion (25°C):	2500 cal/mol	U.S. EPA (1984a)
Conversion factor (air):	1 mg/m³ = 0.265 ppm	Verschueren (1983)

1.3. PRODUCTION DATA

Epichlorohydrin is prepared by a three-step chlorination process in which allyl chloride is produced from propylene and chlorine, followed by hypochlorination and neutralization to yield epichlorohydrin (Blackford, 1978). SRI (1984) estimated that, as of January 1, 1984, annual capacity for domestic production of epichlorohydrin was ~420 million pounds at Dow Chemical (Freeport, TX) and 110 million pounds at Shell Oil Co. at both Deer Park, TX and Norco, LA. Production and importation, as identified in the 1977 TSCA Inventory, are reported in Table 1-1.

TABLE 1-1

Production and Importation of Epichlorohydrin from the 1977 TSCA Inventory*

Company/Location	Importer or Manufacturer	Quantity (lbs)
Marubeni America Corp. New York, NY	importer	1000-10,000,000
Dow Chemical Co. Freeport, TX	manufacturer	100,000,000-500,000,000
Haven Chemical Philadelphia, PA	manufacturer	100,000-1,000,000
Shell Oil Co. Deer Park, TX Norco, LA	manufacturer manufacturer	100,000,000-500,000,000 50,000,000-100,000,000
Mitsubishi International Corp. New York, NY	importer	100,000-1,000,000
Nichimen Co., Inc. New York, NY	importer and manufacturer	10,000-100,000
Hercules, Inc.	importer	classified
Other/unspecified	NR	100,000-1,000,000

*Source: U.S. EPA, 1984b

NR = Not reported

1.4. USE DATA

Epichlorohydrin is a highly reactive akylating agent because of the highly strained nature of its epoxide ring. This reactivity lends itself to the widespread use of epichlorohydrin as an intermediate in a wide variety of chemical manufacturing processes. The major use of epichlorohydrin is in the production of epoxy resins such as those used in coatings, adhesives and plastics; this accounted for 53% of domestic epichlorohydrin consumption in 1977 (Blackford, 1978). Blackford (1978) also estimated that consumption of epichlorohydrin for synthetic glycerine manufacture in 1977 accounted for 25% of epichlorohydrin consumption. Other uses that account for an additional 15% of epichlorohydrin consumption include textiles (fiber modification), paper, inks and dyes, anion-exchange resins, solvents, surfactants, rubber elastomers and starch modifiers (U.S. EPA, 1984a). Epichlorohydrin is also listed as an inert ingredient in pesticidal formulations (Federal Register, 1971).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The fate of epichlorohydrin in aquatic media is governed by its ability to undergo chemical, photochemical and biological transformations, as well as partitioning (transport) from the water column into air or sediment. Based upon its relatively high WS and vapor pressure, epichlorohydrin is expected to partition readily into both water and the atmosphere, rather than sediments. Experimental data are lacking on the affinity of epichlorohydrin for aquatic sediments. An estimate of this property can be made, however, using a regression equation developed by Kenaga and Goring (1980) for deriving the K_{oc}. This equation states that log K_{oc}=3.64-0.55 (log WS)$\pm$1.23 orders of magnitude. Using this approach, a K_{oc} value of ~100 (range 0.57-166) is obtained at a WS value of 66,000 mg/ℓ, indicating a low potential for adsorption to sediments. Based upon its high vapor pressure, epichlorohydrin would be expected to volatilize rapidly from aquatic systems. An evaporation half-life of 2.37 days has been estimated from a 100 cm deep body of water containing 1 ppm of epichlorohydrin at 20°C (U.S. EPA, 1984a). In aquatic media, chemical processes including hydrolysis, volatilization, and reaction of the epoxide moiety with various chemical species appear to govern the fate of epichlorohydrin. Bronsted et al. (1929) reported a hydrolytic half-life of 8 days in distilled water at 20°C. Ross (1950) noted that hydrolysis at 37°C was more rapid in a sodium acetate/acetic acid buffer system (pH 4.6) than in an unbuffered system. At 24 and 48 hours, 52.0 and 76.6%, respectively, of the epichlorohydrin had reacted in the buffer; whereas, in the unbuffered system 36.5 and 59.0% had reacted at 24 and 48 hours, respectively.

Neither of these studies reported the products of epichlorohydrin hydrolysis; however, the initial product of any hydrolytic reaction involving the epoxide group is expected to be 3-chloro-1,2-propanediol. The epoxide group may also react with chloride ion to form 1,3-dichloro-2-propanol with a rate constant of 1×10^{-3} M^{-1} sec^{-1} (Santodonato et al., 1980). Using the concentration of chloride ion in seawater of 18,890 ppm (Weast, 1978), the half-life for the reaction is ~1.5 days.

Aqueous phase oxidation or photodegradation under environmental conditions are not expected to be significant factors in the aquatic fate of epichlorohydrin; this is due to the lack of free radical initiators and because UV absorption at environmentally relevant wavelengths (>290 nm) is expected to be low.

Bridie et al. (1979a) reported that 3% of the BODT was consumed in a 5-day incubation of epichlorohydrin with sewage seed. Acclimated sewage seed consumed 14% of the BODT in the same timespan. Matsui et al. (1975) reported a rapid dissipation of epichlorohydrin from an aerated acclimated sludge inoculum (89% of the COD was lost in 24 hours) but most of this was attributed to volatilization.

Data pertaining to the bioconcentration of epichlorohydrin in aquatic organisms were not located in the available literature cited in the Appendix. Epichlorohydrin is very soluble in water (6.58% at 20°C), which would indicate that there is very limited potential for bioconcentration.

2.2. AIR

As discussed in Section 2.1., partitioning to the atmosphere predicated on the physical properties of epichlorohydrin is expected to be a dominant factor in its environmental fate. No experimental data regarding the atmospheric fate of epichlorohydrin were located. U.S. EPA (1980) estimated

that reaction with hydroxyl radical in the atmosphere would occur, however, with a rate constant of 2×10^{-12} cm^3 $molecule^{-1}$ sec^{-1}. An atmospheric residence time of 5.8 days was estimated, and direct atmospheric photolysis was not thought to be probable; however, Dilling et al. (1976) studied the photodegradation of epichlorohydrin in simulated sunlight (wavelength $\geq$290 nm) in an atmosphere containing 5 ppm nitric oxide (to simulate smog-like conditions), and reported a degradation half-life of 16 hours.

2.3. SOIL

Specific data regarding the fate and transport of epichlorohydrin were not located in the available literature cited in the Appendix. Because of the high WS and vapor pressure of epichlorohydrin, residence times in soil are probably low. Based solely on partitioning considerations, epichlorohydrin is expected to be mobile in soils. Estimation methods developed by Kenaga and Goring (1980) indicate that the soil adsorption potential of epichlorohydrin is low (see Section 2.1.). An estimation method developed by Briggs (1973) also suggests that epichlorohydrin would be mobile in soils, preferring water to the soil column. The EXAMS mathematical environmental model predicts that soil sorption would be a minor mechanism of epichlorohydrin fate at a waste disposal site and that unconfined landfills and lagoons would release virtually all of the epichlorohydrin present to surface waters (U.S. EPA, 1984a). In a train derailment that occurred in 1978 in West Virginia, in which >20,000 gallons of epichlorohydrin were spilled (Chemical Week, 1978), well water in the spill area was reported to contain 75 ppm of epichlorohydrin, which led to the closing of the wells of the city of Point Pleasant at the site of the accident (U.S. EPA, 1978). None of the above theoretical discussions of the behavior of epichlorohydrin

in the environment consider the chemical reactivity of the chemical, particularly at the epoxide center. Given the wide application of epichlorohydrin as a chemical intermediate, reactions with various soil constituents may comprise a major component of the fate of the compound in soil. Data pertaining to the biodegradation of epichlorohydrin by soil microorganisms were not located in the available literature cited in the Appendix.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET Data Base notes the detection of epichlorohydrin at 3 ppm in the effluent of American Aniline Co., Calvert City, KY. Two industrial spills resulting from train accidents have resulted in release of epichlorohydrin to waterways. In 1963, 5000 gallons of epichlorohydrin were spilled into the New River at South Fayette, West Virginia (Gillenwater, 1965). In 1978, in Point Pleasant, West Virginia, a train accident involving the release of >20,000 gallons of epichlorohydrin (Chemical Week, 1978) resulted in contamination of city well water at levels up to 75 ppm, nearest the spill area. This led to closure of the city's wells (U.S. EPA, 1978). Because of its high soil mobility, exposure by consumption of contaminated groundwater may be a potential cause for concern when epichlorohydrin is disposed in solid waste.

3.2. FOOD

Pertinent data regarding exposure to epichlorohydrin in food were not located in the available literature cited in the Appendix. Because of its high water solubility, epichlorohydrin is not expected to accumulate in fish or other aquatic food species. Epichlorohydrin is listed as an inert ingredient in pesticidal formulations applied to growing crops (Federal Register, 1971). Although exempted from the requirement for a tolerance, the presence of epichlorohydrin in food crops from pesticide use cannot be discounted. Also, epichlorohydrin-derived resins have been approved for several food uses by the FDA, which could lead to contamination if traces of epichlorohydrin remain in the resin (U.S. EPA, 1984a)

3.3. INHALATION

Because of the high volatility of epichlorohydrin at ambient temperatures, inhalation of epichlorohydrin in the vapor phase is a likely route of exposure, especially in the workplace under uncontrolled conditions. Oser (1980) reported that workers in two plants that manufacture epichlorohydrin were exposed at levels well below the Federal OSHA standard of 5 ppm (8-hour TWA), which was in effect at the time of the study. The highest levels of epichlorohydrin (0.3 ppm) (one sample at each plant) were found in personal air samples (8-hour TWA) of tank car loaders. Chemical operators were exposed to levels ranging from nondetectable to 0.4 ppm (mean levels 0.2 ppm), and samples from shift foremen contained levels ranging from nondetectable to 0.3 ppm (mean levels of nondetectable and 0.1 ppm) at the two plants. At five plants using epichlorohydrin in the manufacture of resins, six of ten sample categories assayed resulted in mean values for epichlorohydrin below the analytical detection limit. Of the others, only a single general sample in a pump room was >0.1 ppm (1.5 ppm). It was noted that epichlorohydrin production facilities are outdoors, with automated operations monitored from a control room. Operators are only in the production areas for routine inspections, product sampling and occasional maintenance. Levels of up to 4.69 ppm (7-hour TWA) epichlorohydrin have been detected in a glycerin-producing unit (NIOSH, 1976). As reviewed by Federal Register (1983), SAI (1981) estimated that 10.6 million people live within 12.5 miles of facilities producing and using epichlorohydrin, with estimated levels in air ranging from 0.0001 $\mu g/m^3$ (0.000026 ppb) to 50 $\mu g/m^3$ (13 ppb). Amoore and Hautala (1983) noted that epichlorohydrin has an odor threshold in air of 0.93 ppm and estimated that <50% of a "distracted" exposure group would be likely to detect epichlorohydrin at the TLV of 2 ppm (8-hour TWA).

3.4. DERMAL

Pertinent data regarding dermal exposure to epichlorohydrin were not located in the available literature cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Toxicity studies (Chapter 5) indicate that absorption of epichlorohydrin by humans and laboratory species occurs readily following inhalation, oral ingestion or dermal contact.

Weigel et al. (1978) administered ^{14}C-epichlorohydrin in corn oil to CD rats (n=21 of each sex) at 10 mg/kg as a single oral dose and recovered maximum tissue concentrations at 2 and 4 hours postexposure in males and females, respectively. Less than 10% of the administered dose remained in the digestive tract at 8 hours after treatment and fecal excretion was <4%. Therefore, rapid and efficient gastrointestinal absorption is indicated. Smith et al. (1979) reported ~100% absorption of epichlorohydrin within 72 hours of single gavage doses at 1 or 100 mg/kg in F344 rats. Rossi et al. (1983a) treated male Swiss mice with a single dose or seven daily doses of epichlorohydrin by gavage at 50 or 200 mg/kg bw and measured blood concentrations of the toxicant. Single doses at 50 mg/kg bw resulted in blood levels below detectable limits (50 ng/mℓ). At the higher dose, epichlorohydrin in the blood reached a maximum level of 500 ng/mℓ within 5 minutes and was nondetectable at 20 minutes after treatment. Because of the rapid uptake and metabolism of epichlorohydrin, seven repeated doses had little effect on the kinetic profile from that determined for single doses.

Smith et al. (1979) exposed rats by inhalation to epichlorohydrin at 1 and 100 ppm in air for 6 hours. Plasma levels, determined after exposure was terminated, were 0.46 and 27.8 µg epichlorohydrin/ℓ, respectively, with uptake determined to be 15.48 and 1394.0 µg/hour at the low and high exposure levels. The total absorbed doses were 0.37 and 33.0 mg/kg. These data indicate that absorption efficiency was ~40-45% (15.48 µg/hour

absorbed ÷ 35 µg/hour inhaled) and was not greatly decreased at exposure levels as high as 100 ppm epichlorohydrin.

A Russian study (Kremneva and Tolgskaya, 1961) reported toxicity and death of mice that had their tails immersed in epichlorohydrin for a single 1-hour exposure or 20-30 minutes/day for 2 or 3 consecutive days. Dermal absorption may be a significant route of exposure.

4.2. DISTRIBUTION

The distribution of ^{14}C-epichlorohydrin was studied in male and female CD rats treated by gavage with a single 10 mg/kg bw dose (Weigel et al., 1978). Three rats of each sex were sacrificed at 2, 4, 8, 12, 24, 48 and 72 hours after dosing and levels of ^{14}C were determined in most organs, blood, fat, muscle and skin. The highest levels of radiolabel occurred in the kidneys, liver, pancreas, spleen and adrenal. The levels in other organs (heart, lung, brain, muscle, fat, skin and gonads) were near or less than blood levels. Maximum tissue levels were reached within 2 hours in males and 2-8 hours after treatment in females, depending on the tissue. At 72 hours after treatment, residual radioactivity was highest in the kidneys, liver, muscle, skin and blood. Smith et al. (1979) reported a similar pattern with high levels of epichlorohydrin in the stomach, small intestine, kidney, large intestine and liver at 3 hours after a single 100 mg/kg bw dose by gavage.

Smith et al. (1979) determined the tissue distribution of epichlorohydrin following inhalation exposure (100 ppm for 6 hours) and compared these data with distribution kinetics following oral exposure. At the end of the 6-hour exposure, epichlorohydrin levels were greatest in the nasal turbinates, with decreasing levels in the large intestine, kidney, and liver. At 3 hours postexposure, the highest levels of epichlorohydrin were

detected in the liver, kidney, large intestine and small intestine. The authors suggested that the initial high levels of epichlorohydrin in the stomach and nasal turbinates (primary contact tissues) following oral and inhalation exposure, respectively, result in route specific toxicity.

4.3. METABOLISM

Epichlorohydrin appears to be metabolized quite rapidly following absorption. Rossi et al. (1983a) reported that epichlorohydrin was undetectable in the blood of mice within 20 minutes of a single 200 mg/kg bw oral dose. The plasma epichlorohydrin concentration rose rapidly after treatment, reaching a maximum within 5 minutes, but the parent compound was apparently metabolized and plasma levels dropped below detection limits by 20 minutes postexposure. The half-life of epichlorohydrin was ~5 minutes while that for α-chlorohydrin was 50-60 minutes. Migliore et al. (1982a) confirmed the rapid metabolism of epichlorohydrin to α-chlorohydrin, noting that the maximum diol level was reached within minutes (mice given 200 mg/kg bw intraperitoneally) and epichlorohydrin was not detectable.

Smith et al. (1979) recovered urinary metabolites from male F344 rats given single oral doses (1 or 100 mg/kg bw) or inhaling epichlorohydrin (1 or 100 ppm for 6 hours). Although metabolites were not identified, seven compounds were recovered in the urine of orally treated rats, and six urinary metabolites were found following inhalation exposure. Van Duuren (1977) suggested that the metabolism of epichlorohydrin proceeded by oxidation to glycidol, glycidaldehyde and epoxypropionic acid. Jones and O'Brien (1980) reported, however, that formation of α-chlorohydrin was favored over glycidol formation. Rossi et al. (1983a) confirmed the production of α-chlorohydrin from epichlorohydrin, reporting increasing blood α-chlorohydrin levels as epichlorohydrin levels decreased.

Based on their similar toxic effects, Jones et al. (1969) postulated that epichlorohydrin was metabolized by epoxide hydrolysis to α-chlorohydrin. Metabolism of α-chlorohydrin resulted in 2,3-dihydroxypropyl-5-cysteine and N-acetate. In later studies (Jones and Fakhouri, 1979; Fakhouri and Jones, 1979), four urinary metabolites of epichlorohydrin were identified. Following direct conjugation with glutathione and subsequent hydrolysis or secondary glutathione conjugation reactions, bis-mercapturic and mercapturic acids result. These conjugates were the major urinary metabolites. Other nonconjugated metabolites, isolated as minor components, were β-chlorolactic acid and oxalic acid. Oxalic acid is suspected of causing renal toxic effects through the deposition of calcium oxalate in renal tubules. A review of proposed metabolic pathways of epichlorohydrin is presented in Figure 4-1.

Jones and Fakhouri (1979) indicated that epichlorohydrin could react directly with cellular components, rather than glutathione conjugate contributing to its mutagenicity (Section 5.2.). Andersen et al. (1980) reported that a dose at 0.64 mmole epichlorohydrin/kg bw reduced hepatic glutathione by 47% in male Holtzman rats by 2 hours post-treatment. Serrentino et al. (1983) reported that epichlorohydrin could inhibit cytochrome P-450 and aminopyrine N-demethylase activity in in vitro hepatic systems, probably through direct binding. In vivo, cytochrome P-450 was significantly reduced in microsomes from the liver, kidney, testis, lung and small intestine of male rats dosed by gavage at 0.846 mmol/kg (Moody et al., 1982). It was not reported if this decrease was due to metabolic depletion of cytochrome P-450 by epichlorohydrin or was a result of the alkylating effects of the toxicant. Spearman and Leibman (1983) reported that glutathione conjugation of epichlorohydrin occurred with liver and lung cytosol

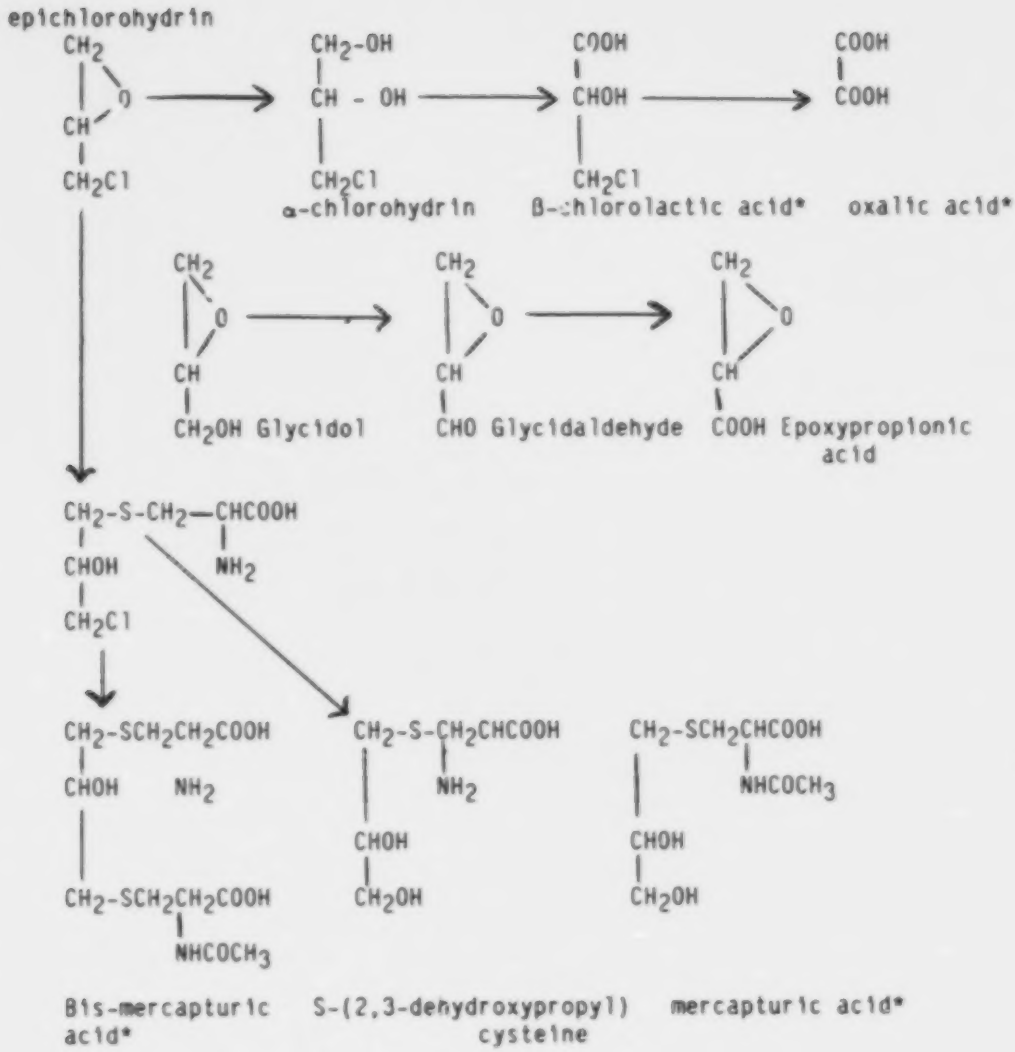


FIGURE 4-1

Proposed Metabolic Pathways of Epichlorohydrin

*Major Urinary Metabolites

preparation and was lower in females than in males, and aged rats compared with young animals. Spearman and Leibman (1983) suggested that aged humans, particuarly females, may be at increased risk of developing health effects from epichlorohydrin exposure, provided humans show a similar decreased ability to conjugate the epoxide as demonstrated in rats.

4.4. EXCRETION

The major route of excretion for metabolites of orally administered ^{14}C-epichlorohydrin was through the urine. Weigel et al. (1978) administered a single dose of epichlorohydrin at 10 mg/kg by gavage to male and female CD rats, and collected excreta for 72 hours. Urinary radioactivity accounted for 38-40% of the administered compound. Elimination of radioactivity in the expired air as $^{14}CO_2$ accounted for 18-21% of the administered dose during the first 24 hours. The elimination of substantial amounts of $^{14}CO_2$ during the early post-treatment period (most within 8 hours) corroborates the rapid and extensive metabolism of epichlorohydrin. Fecal elimination accounted for <4% of the administered radioactivity during 72 hours, which could represent unabsorbed parent compound or biliary metabolites.

Smith et al. (1979) determined excretion kinetics for epichlorohydrin in rats following oral and inhalation exposure. Epichlorohydrin was administered by a single oral dose at 1 or 100 mg/kg bw or by a 6-hour inhalation exposure at 1 or 100 ppm. During the 72 hours from the start of exposure, 46-56% of the radioactivity was recovered in the urine and 25-42% was expired as $^{14}CO_2$. Fecal excretion accounted for 2-6% of the radioactivity. Excretion kinetics did not appear to be affected by route of exposure. None of the metabolites recovered represented unchanged epichlorohydrin.

Excretion of metabolites of epichlorohydrin in the urine was a biphasic process. The half-times of the fast and slow phases of elimination were 1.5 and 26.4 hours while the respective rate constants were 0.55 and 0.26 $hour^{-1}$ (Smith et al., 1979).

5. EFFECTS

5.1. CARCINOGENICITY

An epidemiology study of 864 present and retired Shell Chemical Company employees exposed to epichlorohydrin during its production and use from 1945-1965 was conducted by Enterline and coworkers (Enterline, 1977; Enterline and Henderson, 1978; Enterline et al., 1979; Enterline and Hartley, 1981; Enterline 1980, 1981, 1982). Mortality records for the cohort were studied through 1979. During early reports, 9 deaths among 52 deceased workers were due to lung and respiratory cancer; a significant ($p<0.05$) increase compared with the 6-7% expected. During later studies (total of 65 deaths), the difference between observed and expected respiratory tract cancers were not significantly increased. Enterline and Hartley (1981) reported a SMR of 119.5 for respiratory cancer among the cohort through 1979. Enterline (1981) reported 10 observed and 8.7 expected respiratory cancer deaths (Table 5-1). The researchers, however, suggested that epichlorohydrin should be viewed as a human carcinogen based on the suggestive epidemiological evidence and animal carcinogenicity data.

A report on Dow Chemical Company workers (Shellenberger et al., 1979) who were exposed to epichlorohydrin during the production of glycerine and epoxy resins showed no apparent increase in mortality. Although Shellenberger et al. (1979) suggested no association between epichlorohydrin exposure and cancer death, caution should be taken in accepting this conclusion. The cohort consisted of primarily young workers (62% were <40 years of age) and most (63%) had <10 years latency since the onset of exposure. This combination of factors results in an inadequate measure of the effects of chronic epichlorohydrin exposure on mortality.

TABLE 5-1

Human

Agent: Epichlorohydrin*

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (P value)
Occupational (primarily inhalation)	864	national mortality rates	M.R.	M.R.	>3 months	respiratory	cancer	10[a]	8.7[a]	1.15
						blood	leukemia	2	1.0	2.0

QUALITY OF EVIDENCE

Strengths of Study: A cohort of occupationally exposed workers was identified and a follow-up conducted. A latency of at least 15 years was allowed.

Weaknesses of Study: The level of epichlorohydrin exposure was not determined. The number of deaths was limited, which prevents an adequate test of carcinogenicity

Overall Adequacy: Limited

Comments: Enterline and Henderson (1978) reported higher SMR values for respiratory cancer and leukemia but these differences were not strengthened in the 1981 follow-up study.

[a]Source: Enterline, 1981

[b]Excluding isopropyl alcohol workers, 8 cases were observed and 6.53 expected; nonsignificant

MR = Not reported

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Tassignon et al. (1983) conducted a mortality study of workers exposed to epichlorohydrin in four European plants producing epichlorohydrin, epoxy resins, glycerin or other epichlorohydrin derived chemicals. A cohort of 606 workers having $\geq$1 year of exposure and $\geq$10 years of latency was identified. This study reported four cancer deaths (various sites) while five were expected. The lack of association between exposure to epichlorohydrin and increased cancer death cannot be regarded as conclusive evidence. This study (Tassignon et al., 1983) allowed a short latency period to elapse and because ofthe low average age (42 years) of the workers. The potential carcinogenicity of epichlorohydrin was, there- fore, not adequately tested.

In animals, the carcinogenicity of epichlorohydrin was tested by Laskin et al. (1980) in male rats exposed by inhalation. In two parallel studies, groups of 100 and 40 Sprague-Dawley rats were exposed at 100 ppm for 6 hours daily on 30 consecutive days. Following these subchronic exposures, rats were observed for their lifetime. Neoplastic lesions of the nasal cavity, a relatively rare spontaneous tumor in rats, developed between days 330 and 933 from the onset of exposure. Of the 140 total rats, 18 developed benign or malignant nasal tumors, 15 of which were squamous cell carcinomas (Table 5-2). Histologically, many of the squamous carcinomas involved the cranial bones but remote metastasis was not observed. Two nasal papillomas and a bronchial papilloma were also observed. Control rats (1920 historical controls) had no nasal tumors.

In additional studies by Laskin et al. (1980), groups of 100 male Sprague-Dawley rats were exposed at 10 or 30 ppm for 6 hours/day, 5 days/ week over their lifetimes. Weight gain in the high-dose group and survival in both groups was initially decreased compared with controls. Mortality

TABLE 5-2

Animal

Agent: Epichlorohydrin*

Exposure Route	Species/ Strain	Sex	Concentration (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle	Target Organ	Tumor Type	Tumor Incidence (p value)
Inhalation	rat/ Sprague-Dawley	M	100 ppm 6 hours/day	30 days	1008	>99	air	nasal epithelium	squamous cell carcinoma	15/140
NA	rat/ Sprague-Dawley	M	0 ppm	NA	NR	NA	air	nasal cavity	squamous cell carcinoma	0/1920
Inhalation	rat/ Sprague-Dawley	M	30 ppm 6 hours/day, 5 days/week	952 days	952 days	>99	air	nasal cavity	squamous cell carcinoma	1/100
Inhalation	rat/ Sprague-Dawley	M	10 ppm 6 hour/day, 5 days/week	952 days	952 days	>99	air	nasal cavity	any	0/100
NA	rat/ Sprague-Dawley	M	0 ppm	NA	952 days	NA	air	nasal cavity	any	0/100
NA	rat/ Sprague-Dawley	M	NA	NA	952 days	NA	NA	nasal cavity	any	0/50

QUALITY OF EVIDENCE

Strengths of Study: A large number of animals were used in each group and appropriate control groups were included for comparison. An appropriate route of administration was used. Complete histopathological autopsies were performed.

Weakness of Study: Both sexes should have been tested. No statistical calculations were performed on the data.

Overall Adequacy: Adequate

Comments: The authors noted that the overall dose at 30 ppm for lifetime was greater than at 100 ppm for 30 days but the subchronic, higher exposure level showed a carcinogenic response. Toxic effects prevented chronic exposures at higher levels.

*Source: Laskin et al., 1980

NA= Not applicable; NR = not reported

among both epichlorohydrin exposed groups was 100% by 136 weeks. Severe lung congestion and pneumonia were observed in treated rats. No neoplastic lesions were seen in any rats exposed at 10 ppm, and two tumors (a nasal papilloma and squamous cell carcinoma) occurred among rats in the high-dose group (see Table 5-2). None of the control rats (100 air-exposed, 50 untreated) developed nasal tumors.

Konishi et al. (1980) conducted a carcinogenicity study of epichlorohydrin in male Wistar rats treated orally. Groups of 18 animals each were treated at 0 (control group 1), 375 (group 2), 750 (group 3) or 1500 ppm (group 4) epichlorohydrin in the drinking water. Between weeks 60 and 81, all treatment groups received untreated water intermittently because of poor rat health. The total doses of epichlorohydrin per rat were 0, 5.0, 8.9 and 15.1 g in groups 1-4, respectively. Dose related decreased weight gain was reported. All surviving rats were killed and autopsied at 81 weeks. Histological findings revealed a dose related increase in forestomach tumors, ranging from hyperplasias to papillomas and carcinomas. The average number of forestomach tumors per rat was 0, 5.6, 9.9 and 32.8 in groups 1-4, respectively. In group 2 (375 ppm treated), seven of nine effective animals had squamous hyperplasia but no more progressive tumors. Of the 10 effective rats in group 3 (750 ppm), 9 hyperplasias, 1 papilloma and 1 carcinoma were reported (Table 5-3). All 12 rats (100% incidence) in group 4 (1500 ppm) had seven hyperplasias of the forestomach with seven and two papillomas and carcinomas, respectively, being identified. In addition to the forestomach carcinomas in group 4 (2/12), squamous cell carcinomas of the oral cavity were seen in 2 of 12 rats from this group. These data indicate that epichlorohydrin has carcinogenic activity in rats following oral ingestion, showing a dose related progression of tumorigenicity from preneoplastic states to carcinoma but no metastases were observed in any of the test

TABLE 5-3

Animal

Agent: Epichlorohydrin*

Exposure Route	Species/ Strain	Sex	Concentration (ppm)	Duration of Treatment (days)	Duration of Study (days)	Purity of Compound (%)	Vehicle	Target Organ	Tumor Type	Tumor Incidence (p value)
Oral	rat/Wistar	M	1500	567	567	NR	drinking water	forestomach	squamous cell carcinoma	2/12
									papilloma	7/12
Oral	rat/Wistar	M	750	567	567	NR	drinking water	forestomach	squamous cell carcinoma	1/10
									papilloma	1/10
Oral	rat/Wistar	M	375	567	567	NR	drinking water	forestomach	squamous cell carcinoma	0/9
									papilloma	0/9
Oral	rat/Wistar	M	0	567	567	NR	drinking water	forestomach	squamous cell carcinoma	0/10
									papilloma	0/10

QUALITY OF EVIDENCE

Strengths of Study: An appropriate route of administration was used. Exposure was for a long duration at different levels. Complete autopsies were performed.

Weakness of Study: Only male rats were tested. No statistics were performed. The purity of epichlorohydrin was not specified.

Overall Adequacy: Adequate

Comments: Chronic toxic effects prevented testing at a higher dose level, which may have produced a higher incidence of forestomach carcinomas.

*Source: Konishi et al., 1980

NR = Not reported

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animals. Statistical analyses were not performed on the incidence of forestomach tumors. This study could have provided more convincing evidence of carcinogenicity if larger animal numbers were used and if exposure/observation periods were for the lifetime of the rat.

In another study, van Esch (1982) reported forestomach tumors in male and female Wistar rats after administration 2 or 10 mg/kg bw/day epichlorohydrin by gavage. The treatments were given to groups of 50 animals of each sex for 104 weeks. Mortality among female rats was high in all groups during the first 12 months of the study, which was due to high fiber diet but was corrected so that survival at 2 years was 40-44%. The incidence of forestomach carcinomas among males treated at 10, 2 and 0 mg epichlorohydrin/kg bw/day was 35/47, 6/49 and 0/50, respectively. In females, the incidence of forestomach carcinomas was 24/39, 2/44, and 0/47 in high-dose, low-dose, and control groups, respectively (Table 5-4). Carcinomas were diagnosed among rats dying (or killed) from 20-30 months after the onset of exposure. Before this interval, forestomach papillomas and hyperplasia were reported. The incidence of forestomach carcinomas was significantly ($p<0.01$) elevated in male and female rats treated at 10 mg/kg bw/day. The Carcinogen Assessment Group (U.S. EPA, 1984c) regarded these data as preliminary evidence that suggest epichlorohydrin conclude carcinogenic to rats when ingested.

Henschler et al. (1984) conducted carcinogenicity studies of technical trichloroethylene and various samples fortified with epichlorohydrin (used as a stabilizer for trichlorethylene). Groups of Swiss mice of both sexes were treated by gavage for 18 months and observed for an additional 28 weeks. Males received 19.2 mg epichlorohydrin/kg bw/day (2.4 g/kg/day of 0.8% solution with trichlorethylene) and females were given 14.4 mg epichlorohydrin/kg bw/day (1.8 g/kg/day of 0.8% solution with trichlorethylene).

TABLE 5-4

Animal

Agent: Epichlorohydrin[a]

Exposure Route	Species/ Strain	Sex	Concentration (mg/kg/day)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound (%)	Vehicle	Target Organ	Tumor Type	Tumor Incidence
Oral (gavage)	rat/Wistar	M	10	104	130	NR	water	forestomach	squamous cell carcinoma	35/47[b]
	rat/Wistar	F	10	104	130	NR	water	forestomach	squamous cell carcinoma	24/39[b]
Oral (gavage)	rat/Wistar	M	2	104	130	NR	water	forestomach	squamous cell carcinoma	6/49
	rat/Wistar	F	2	104	130	NR	water	forestomach	squamous cell carcinoma	2/44
Oral (gavage)	rat/Wistar	M	0	104	130	NA	water	forestomach	squamous cell carcinoma	0/50
	rat/Wistar	F	0	104	130	NA	water	forestomach	squamous cell carcinoma	0/47

QUALITY OF EVIDENCE

Strengths of Study: Male and female rats were treated. The duration of treatment and observation period were long. The number of animals used allowed sufficient statistical comparisons. An appropriate route of administration was used.

Weakness of Study: This study was available in the U.S. EPA (1984a) document and was not accepted or published in the open literature

Overall Adequacy: Adequate

Comments: Epichlorohydrin was administered by gavage using water as the solvent.

[a]Source: van Esch, 1982

[b]Significantly different ($p<0.01$) from controls

NR = Not reported; NA = not applicable

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In all groups receiving epichlorohydrin, the incidence of forestomach papillomas and carcinomas was significantly increased, while mice receiving amine-stabilized trichloroethylene had no significant increase in forestomach tumors. These data support the results of Konishi et al. (1980) and van Esch (1982) that epichlorohydrin induces forestomach tumors in rodents following oral exposure.

Skin carcinogenicity studies of epichlorohydrin were conducted by Van Duuren et al. (1974). Groups of 50 female ICR/Ha Swiss mice were painted on the dorsal skin 3 times/week with 2 mg epichlorohydrin in 0.1 mℓ acetone. The study was conducted for 580 days with no skin papillomas or carcinomas occurring among treated mice. Epichlorohydrin was not considered a complete skin carcinogen. Weil et al. (1963) also found negative results when one "brushful" of undiluted epichlorohydrin was painted on the chipped dorsal skin of 40 C3H mice 3 times/week for life. At 17 months of exposure, 30 mice were alive and one mouse survived for 25 months.

Van Duuren et al. (1974) conducted a subcutaneous injection assay and a peritoneal injection assay of epichlorohydrin in female ICR/Ha Swiss mice. Epichlorohydrin was injected subcutaneously at 1 mg in 0.05 mℓ tricaprylin once weekly for up to 580 days. Six of 50 treated mice developed local sarcomas and one had a local adenocarcinoma ($p<0.05$); however, only one mouse of 50 vehicle treated controls developed a local sarcoma (Table 5-5). At 300 days into the study, only two treated mice had developed local sarcomas, the first tumor being detected at 126 days (Van Duuren et al., 1972). In the intraperitoneal study, 30 mice received 1 mg epichlorohydrin in 0.05 mℓ tricaprylin once weekly for 450 days. No local sarcomas developed in treated mice but 11 lung papillomas were reported. Vehicle control mice, however, developed 10/30 lung papillomas, and one developed a

TABLE 5-5

Animal

Agent: Epichlorohydrin*

Exposure Route	Species/ Strain	Sex	Concentration	Duration of Treatment (days)	Duration of Study (days)	Purity of Compound (%)	Vehicle	Target Organ	Tumor Type	Tumor Incidence
Subcutaneous	mouse/ ICR/Ha Swiss	F	1 mg/weekly	580	580	Distilled pure	tricaprylin	skin	local sarcoma or adenocarcinoma	7/50[b]
Subcutaneous	mouse/ ICR/Ha Swiss	F	0 mg/weekly	580	580	NA	tricaprylin only	skin	local sarcoma or adenocarcinoma	1/50

QUALITY OF EVIDENCE

Strengths of Study: Epichlorohydrin was administered for the lifetime of the mice. A vehicle control group was included for comparison. Statistical analyses were performed.

Weakness of Study: The relevance of subcutaneous injection and the development of local tumors to natural-exposure-route carcinogenicity is questionable.

Overall Adequacy: Limited

[a]Source: Van Duuren et al., 1974

[b]Significantly different ($p<0.05$) from control.

NA = Not applicable

local sarcoma. Epichlorohydrin was effective in producing local tumors by subcutaneous injection but had no notable effect when injected intraperitoneally.

5.2. MUTAGENICITY

The number of mutagenicity studies of epichlorohydrin is too large to cover completely in a review of this nature. Selected studies representing the data base are summarized in Table 5-6. Studies were conducted in prokaryotic and eukaryotic organisms using various assays. Generally, epichlorohydrin was found to be mutagenic (U.S. EPA, 1984a). Prokaryotic assays for gene mutations and repairable genetic damage in bacteria were conducted. Mutation studies were also done in yeast, Drosophila sp. and mammalian cells. Chromosomal aberration studies were done using human and other mammalian cells following in vitro and in vivo exposure to epichlorohydrin.

In microbial test systems, primarily the Ames' assay using Salmonella typhimurium, epichlorohydrin has shown direct mutagenic activity (Elmore et al., 1976; Sram et al., 1976; Bridges, 1978; McMahon et al., 1979; Eder et al., 1980). Positive mutagenicity was demonstrated most convincingly in base-pair sensitive strains of S. typhimurium (Table 5-6). Andersen et al. (1978) reported 352, 500, 650, 800 and 1200 revertants/plate at 0.5, 1.0, 1.5, 2.0 and 2.5 μmoles/plate, respectively, in S. typhimurium strain TA100 in the absence of metabolic activation. Eder et al. (1980) reported fewer mutant reversions in S. typhimurium strain TA100 when S-9 was added to the assay system, than when epichlorohydrin alone was added. In addition to assays using S. typhimurium, assays have been conducted using Escherichia coli (McMahon et al., 1979) and Klebsiella pneumoniae (Voogd et al., 1981; Knapp et al., 1982). Epichlorohydrin was also a positive mutagen in these organisms.

TABLE 5-6

Summary of Selected Mutagenicity Data for Epichlorohydrin

Assay	Indicator/ Organism	Compound and/or Purity	Appli-cation	Concentra-tion or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium	analyt. pure	plate test	1.0 mM	None	+	strain TA100	Elmore et al., 1976
	S. typhimurium	NR	plate test	0.108-540 mM	None	+	strains G46, TA100	Sram et al., 1976
	S. typhimurium	NR	plate test	1000 µg/ml	None	+	strain G46	Bridges, 1978
	S. typhimurium	NR	plate test	<100 µg/ml	None	+	strain TA100	Bridges, 1978
	S. typhimurium	NR	air exposure	1.25-3.0 µg/L air	None	+	strain TA100	Bridges, 1978
	S. typhimurium	NR	air exposure	7 µg/L air	None	+	strain TA1535	Bridges, 1978
	S. typhimurium	NR	agar incor-poration	0.2 µg/cm agar	None	+	strain TA1535	Bridges, 1978
	S. typhimurium	NR	plate test	0.5-2.5 µ moles/plate	None	+	strains TA100, TA1535	Andersen et al., 1978
	S. typhimurium	NR	plate test	NR	None	+	strains G46, TA100, TA1535	McMahon et al., 1979
	S. typhimurium	NR	plate test	NR	None	-	strains TA1537, TA1538, TA98, C3076, D3052 (frame-shift sensitive)	McMahon et al., 1979
	S. typhimurium	99.5%	liquid suspension	NR	±S9	+	strain TA100	Eder et al., 1980
	S. typhimurium	analyt. grade	plate test	0.05-1.0 mM	±S9	+	strain TA100; little to no mutagenicity with metabolic activation	Voogd et al., 1981

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Appli-cation	Concentra-tion or Dose	Activating System	Response	Comment	Reference
Reverse mutation	S. typhimurium	>99%	plate test	1.13 mM	None	+	strains TA100, TA1535	Bartsch et al., 1983
	S. typhimurium	NR	plate test	4.75 mM	None	+	strain TA100	Laumbach et al., 1977
	Escherichia coli	NR	plate test	NR	None	+	strains WP2, WP2uvrA⁻	McMahon et al., al., 1979
	Klebsiella pneumoniae	analyt. grade	plate test	0.2-1.0 mM	None	+		Voogd et al., 1981
Host-mediated	S. typhimurium	NR	ICR mice	50 or 100 mg/kg i.m. injection to mice	NA	+	strains G46, TA100, TA1950	Sram et al., 1976
Forward mutation	Schizosaccharo-myces pombe	99.82%	liquid suspension	0.2-6.4 mM	±S9	+	mutagenic activity was reduced when metabolic activation system was added	Migliore et al., 1982b
Reverse mutation	Saccharomyces cerevisiae	NR	liquid suspension	65 or 130 mM for 5-20	None	+	dose and duration re-lated effect was evident	Vashishat et al., 1980
Mitotic cross-over	S. cerevisiae	NR	liquid suspension	65 or 130 mM for 5-20	None	+	dose and duration re-lated effect was evident	Vashishat et al., 1980
Gene conversion	S. cerevisiae	NR	liquid suspension	65 or 130 mM for 5-20	None	+	dose and duration re-lated effect was evident	Vashishat et al., 1980
Sex-linked	Drosophila	NR	diet	2.6 and 5.1 mM	NA	-	toxicity and lethality occurred	Knapp et al., 1982
Recessive lethal	Drosophila	NR	injection	2.6, 5.1, 25.5 mmoles	NA	+	lowest dose showed bor-derline mutagenicity	Knapp et al., 1982
SCE	CHO cells	NR	liquid medium	50, 100, 200 μM	None	+	toxicity occurred at 200 μM	Kublak et al., 1982

TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Appli-cation	Concentra-tion or Dose	Activating System	Response	Comment	Reference
SCE	Chinese hamster V-79 cells	NR	liquid medium	10-100 µg/ml	None	+	NC	Nishi et al., 1984
Chromosome damage in vitro	mouse lymphoma	NR	liquid medium	0.5, 1.0 mM	None	+	exposure was for 2 hours	Knapp et al., 1982
Chromosome damage	CHO cells HGPRT gene	NR	liquid medium	12-50 µg/ml	None	+	50 µg/ml was toxic	Amacher and Zelljadt, 1984
Chromosome damage	rat hepatocyte	NR	liquid medium	0.3-1.0 mM	None	+	0.3 mM did not increase DNA breaks, other test concentrations increased breaks	Sina et al., 1983
Chromosomal damage, in vivo	mouse bone marrow	NR	i.p. and orally	1-100 mg/kg	NA	+	increased chromosomal breaks, gaps and abnormal cells	Sram et al., 1976
	mice spermatogonia	NR	inha-lation	5, 25, 125 mg/m³ x 120 hours	NA	+	SCE increased frequency	Sram et al., 1981
Dominant Lethal	ICR/Ha mice	NR	i.p.	150 mg/kg	NA	-	No difference in implants or dead fetuses	Epstein et al., 1972
	ICR mice	NR	i.p.	5, 10 or 20 mg/kg	NA	-		Sram et al., 1976
	ICR mice	NR	i.p.	1 or 4 mg/kg x5 doses	NA	-	Repeated dosing increased effect	Sram et al., 1976
	ICR mice	NR	oral	20 or 40 mg/kg	NA	-		Sram et al., 1976
	ICR mice	NR	oral	4 or 16 mg/kgx5 doses	NA	-	Repeated dosing increased	Sram et al., 1976

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TABLE 5-6 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Appli- cation	Concentra- tion or Dose	Activating System	Response	Comment	Reference
Human lympho- cytes, *in vitro*	human	NR	liquid culture	10^{-4} to 10^{-11} M	None	+	10^{-4} M was toxic; dose related chromosomal changes	Kucerova et al., 1976
Human lympho- cytes, *in vitro*	human	NR	liquid culture	10^{-5} to 10^{-11} M	None	+	dose related chromosomal aberrations	Sram et al., 1976
Human lymphocytes, *in vitro*	human	NR	liquid culture	$4x10^{5}$ to $2x10^{-4}$ M	±S9	+	increased SCE; metabolic activation decreased activity	White, 1980
Human lymphocytes, *in vivo*	human	epichloro- hydrin (production)	occupa- tional exposure	workroom levels for 0, 1 and 2 years	NA	+	duration related increase in chromosome aberrations	Kucerova et al., 1977
Human lympho- cytes, *in vivo*	human	epichloro- hydrin	occupa- tional exposure	workroom levels (<0.5 ppm)	NA	+	increased total chromocytes, some aberrations	Picciano, 1979
Human lympho- cytes, *in vivo*	human	epichloro- hydrin	occupa- tional exposure	0.384- 1.0 mg/m³	NA	+	increased frequency of aberrant lymphocytes	Sram et al., 1980, 1983

NA = Not applicable; NR = not reported; NC = no comment

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In the host-mediated assay (Sram et al., 1976), epichlorohydrin induced reverse mutations in S. typhimurium strains G46, TA100, and TA1950. Epichlorohydrin was injected intramuscularly at 50 and 100 mg/kg to female ICR mice previously treated (intraperitoneally) with bacteria. Mice were killed 3 hours after epichlorohydrin treatment and peritoneal fluid was assayed for revertant bacteria. Strains G46, TA100 and TA1950 showed an increased reversion frequency compared with controls but strains TA1951 and TA1952 had similar reversion frequencies.

Migliore et al. (1982b) reported an increased frequency of forward gene mutations in the yeast, Schizosaccharomyces pombe, following exposure to epichlorohydrin at 0.2-3.2 mM. Of a series of aliphatic epoxides tested, epichlorohydrin was the most effective in causing mutations in the yeast. Metabolic activation appeared to reduce the mutagenic activity of epichlorohydrin on yeast. Rossi et al. (1983b) suggested that microsomal epoxide hydrolase initiated detoxification of epichlorohydrin and therefore, reduced its mutagenic potential when an activation system was present. Vashishat et al. (1980) reported that epichlorohydrin induced reverse gene mutation, mitotic crossing-over and gene conversion in the yeast, Saccharomyces cerevisiae. Treatments were at 65 and 130 mM for 5-20 minutes. Dose related and exposure duration related increases in gene alterations were evident.

In Drosophila, Rapoport (1948) reported that the frequency of sex-linked recessive lethal mutations was 0.7% among 526 chromosomes from epichlorohydrin treated flies; the frequency was 0% among 887 chromosomes of control flies. Knapp et al. (1982) reported that epichlorohydrin was not mutagenic to Drosophila when the compound was in the diet. Toxicity and death occurred among flies exposed at 5.1 and 25.5 mM but no sex-linked recessive

lethal mutations were observed. Following injection exposure to epichlorohydrin, however, doses of 2.6, 5.1 and 25.5 mmoles induced recessive lethal mutations. Wurgler and Graf (1981) also found no increase in the frequency of sex-linked recessive lethal mutations in Drosophila fed epichlorohydrin (0.2% dietary level). The frequency of mutations was 0.32, 0.28 and 0.40 in treated, control, and vehicle control groups, respectively.

The mutagenicity of epichlorohydrin has also been demonstrated in mammalian cells cultured in vitro. In mouse lymphoma L5178Y/TK^{+-} cells, epichlorohydrin at 20-60 µg/mℓ induced mutations at the thymidine kinase locus (Moore-Brown and Clive, 1979). The frequency of SCE in CHO cells was increased following treatment with epichlorohydrin at 50 and 100 µM (200 µM was toxic) (Kubiak et al., 1982). Nishi et al. (1984) reported a dose related increase in SCE and 6-thioguanine-resistant mutations in Chinese hamster V79 cells exposed at 10-100 µg epichlorohydrin/mℓ. Amacher and Zelljadt (1984) reported a significant dose related increase in mutations at the hypoxanthine-guanine phosphoribosyl transferase locus of CHO cells exposed to epichlorohydrin at 12-40 µg/mℓ. At 50 µg epichlorohydrin/mℓ, survival was reduced to 10% of controls and the mutant frequency was approximately that of controls. In rat hepatocytes exposed in vitro, single strand DNA breaks were induced by epichlorohydrin at 0.3 and 1.0 mM, while 0.03 mM did not cause a significant increase in breaks (Sina et al., 1983).

Following exposure to epichlorohydrin in vivo, mouse bone marrow cells were used to show several mutagenic effects. The frequency of SCE was increased in bone marrow cells of treated mice (Paika et al., 1981). Migliore et al. (1983) reported no increase in chromosomal aberrations of bone marrow cells from CD1 mice fed single doses of epichlorohydrin at 50 or 200 mg/kg bw. Dabney et al. (1979) exposed groups of 10 male and 10 female

F-344 rats to epichlorohydrin by inhalation at 0, 5, 25 and 50 ppm (6 hours/day; 5 days/week) for 4 weeks. The frequency of chromosomal abnormalities was examined in 200 bone marrow cells per animal. The frequency of chromosomal abnormalities was increased 2-fold in males exposed at 25 and 50 ppm but increases were sporadic and did not show a dose-related response. Male rats exposed at 5 ppm had fewer than one-half the number of chromosomal abnormalities that were seen in controls. No change in bone marrow chromosomal abnormalities were reported in the female rats. Sram et al. (1976) reported increased frequencies of chromosomal breaks and gaps and abnormal cells from bone marrow of mice treated with epichlorohydrin (by i.p. injection at 1-50 mg/kg or perorally at 5-100 mg/kg). Repeated dosing (5 doses in 7 days) enhanced the mutagenic effect of epichlorohydrin. Kliesch and Adler (1983) also reported increased chromosomal changes in bone marrow cells of mice treated with epichlorohydrin. Sram et al. (1981) reported an increased frequency of SCE in spermatogonia and sperm abnormalities in mice exposed to epichlorohydrin by inhalation at 5, 25 and 125 mg/m^3 for 120 hours. In rats, the frequency of aberrant peripheral lymphocytes was increased following inhalation exposure to epichlorohydrin at 5, 25 and 120 mg/m^3 for 8 hours (Sram et al., 1981). In the mouse micronucleus test with erythrocytes, epichlorohydrin (0.0225-0.09 mL/kg intraperitoneally for two doses) did not increase the frequency of micronuclei compared with controls (Kirkhart, 1981).

Using the dominant lethal assay as a test of mutation to parental germ cells, Epstein et al. (1972) reported no difference in the number of implants and dead fetuses between treated (150 mg/kg intraperitoneally) and control groups. Sram et al. (1976) also reported negative results in the dominant lethal assay. Mice were treated by intraperitoneal injection (5,

10, or 20 mg/kg single dose and 1 or 4 mg/kg for 5 doses) or orally (20 or 40 mg/kg, single dose or 5 repeated doses) with no apparent increase in lethal mutants.

Kucerova et al. (1976) conducted mutagenicity studies with cultured human lymphocytes exposed to epichlorohydrin at 10^{-4} to 10^{-11} M for 1 or 24 hours. A dose-related increase in chromosomal aberrations, primarily chromatid and chromosome breaks, was reported. Exposures at 10^{-4} M for 24 hours were toxic, but exposures at 10^{-5} M for 24 hours increased aberrations (9.2/100 metaphases) compared with controls (1.9/100 metaphases). Sram et al. (1976) exposed human lymphocytes in vitro at 10^{-5} to 10^{-11} M epichlorohydrin for 24 hours and reported a dose-related increase in chromosomal breaks, gaps and aberrant cells. Human lymphocytes cultured with epichlorohydrin at $4x10^{-5}$ to $2x10^{-4}$ M showed a significant dose-related increase in SCE frequency (White, 1980). Metabolic activation had a deactivating effect on epichlorohydrin mutagenicity. The frequency of SCE was 6.80-8.65, 9.00-10.80, and 10.25-12.70/cell, respectively, in human lymphocyte cultures exposed at 0, 10^{-8} and 10^{-5} M epichlorohydrin (Carbone et al., 1981). No significant increase in SCE frequency was noted in lymphocyte cultures exposed at 10^{-11} M epichlorohydrin (Carbone et al., 1981). Perocco et al. (1983) reported that epichlorohydrin increased unscheduled DNA synthesis but inhibited thymidine uptake in cultured human lymphocytes.

Exposure to epichlorohydrin in vivo has also been associated with chromosomal changes in humans (Kucerova et al. 1977; Picciano, 1979; Sram et al., 1983). Kucerova et al. (1977) examined blood cell chromosomes of 35 workers before employment, 1 year after starting work and 2 years after their employment. Two hundred metaphases were examined for each employee for each interval. The average frequency of aberrations was 1.37, 1.91 and

2.69% initially. After 1 year of employment and after 2 years of working in epichlorohydrin production, the frequency for workers exposed for 2 years was highly significant ($p<0.0001$). Chromosomal and chromatid breaks were the most common aberration. Picciano (1979) also found a high frequency of chromosomal aberrations (98%) in lymphocytes of 93 workers exposed to epichlorohydrin compared with controls (5.13 total aberrations). Sram et al. (1980, 1983) reported a significant ($p<0.05$) increased frequency of aberrant cells among workers exposed to epichlorohydrin at 0.384-1.0 mg/m^3 for 6 months to 2 years. The frequency of lymphocyte aberrations was 3.12, 2.06 and 1.33% among epichlorohydrin exposed workers, matched controls and the general population, respectively.

5.3. TERATOGENICITY

A study of the teratogenic and embryotoxic effects of epichlorohydrin has been conducted by the Dow Chemical Company using Sprague-Dawley rats and New Zealand rabbits (John et al., 1979, 1983a; Pilny et al., 1979). Pregnant animals were exposed to epichlorohydrin by inhalation at 0, 2.5 or 25 ppm for 7 hours/day on days 6-15 (rats) or 6-18 (rabbits) of gestation. Dams experienced decreased body weight, decreased food consumption and increased resorption rate. No other embryotoxic effects were observed among litters of rats or rabbits exposed to epichlorohydrin. Examinations for gross and histopathological abnormalities revealed no teratogenic effects (John et al., 1983a).

Marks et al. (1982) conducted a teratogenicity study of epichlorohydrin using rats and mice. Pregnant CD rats and CD-1 mice were given epichlorohydrin at 40, 80 and 160 or 80, 120 and 160 mg/kg/day, respectively, on days 6-15 of gestation. Rats and mice treated at the two higher dose levels showed slight signs of toxicity when compared with vehicle controls. No

embryotoxic effects, however, were evident in any epichlorohydrin treated group of either species. Following gross, visceral and skeletal examinations, no treatment related teratogenic effect was evident in either rats or mice.

5.4. OTHER REPRODUCTIVE EFFECTS

A review of the data regarding reproductive effects of epichlorohydrin in humans and laboratory animals has been conducted by Barlow and Sullivan (1982).

Exposure to epichlorohydrin has been associated with antifertility effects in male laboratory animals and in occupationally exposed men (U.S. EPA, 1984a). Hahn (1970) administered 15 mg epichlorohydrin/kg/day orally to male Sprague-Dawley rats for 12 days. Male fertility was determined by placing two pre-estrus females with each male overnight. This process was repeated using different females for 7 nights. The number of uterine implantations among females was used as an index of fertility. The males became infertile following epichlorohydrin exposure. No histological changes of the testes, epididymis, prostrate or seminal vesicle were detected. The infertility was reversible within 1 week of epichlorohydrin treatment.

Cooper et al. (1974) studied the effects of epichlorohydrin when administered orally at 20, 50 or 100 mg/kg to male Wistar rats. Doses of 20 or 50 mg/kg were administered for 5 days and 100 mg/kg was given as a single dose. Males were mated with unexposed females for 10 consecutive weeks. Treatment at 50 mg/kg/day for 5 days caused complete infertility in males for the 10-week mating period while a single dose at 100 mg/kg reduced fertility, but not completely. Infertility was noted for 3 weeks in males treated at 20 mg/kg/day (5 doses).

The effects of inhaled epichlorohydrin on fertility of male rabbits and male and female rats were studied by John et al. (1983b). Groups of 10 rabbits and 30 rats of each sex were exposed at 0, 5, 25 or 50 ppm epichlorohydrin for 6 hours/day, 5 days/week for 10 weeks. Exposed animals were mated with unexposed animals of the opposite sex at various periods during and after exposure to epichlorohydrin. Exposure at 50 ppm for 10 weeks caused infertility in male rats, which was reversible after 2 weeks. Male rats exposed at 25 ppm were not completely infertile, but fewer implantations occurred among females mated by these males. No effect was evident on the reproductive capacity of epichlorohydrin exposed female rats. No apparent effects occurred in male rabbits exposed to 50 ppm epichlorohydrin, and spermatozoa were normal.

Cassidy et al. (1983) reported that epichlorohydrin administered as a single oral dose at 50 mg/kg to male Wistar rats caused a significant increase in sperm having abnormal head morphology. Sperm were examined 11 days after exposure. No effect on the total sperm count was evident in treated males.

Kluwe et al. (1983) reported that sperm concentrations in the epididymis of male F344 rats given a single i.p. injection of 75 mg epichlorohydrin/kg were reduced at 25 and 75 days post-treatment but were not reduced at 3 or 8 days post-exposure. The percentage of abnormal sperm at 25 and 75 days was 3.0 and 12.5%, respectively ($p<0.05$). Epichlorohydrin also caused epididymal and testicular histological changes.

Milby and Whorton (1980) and Milby et al. (1981) conducted a clinical study of testicular function among male epichlorohydrin production plant workers. A group of 128 epichlorohydrin exposed workers was examined and compared with a reference group of 90 unexposed chemical plant workers.

Semen samples were taken to determine sperm counts and blood samples were taken for measurement of the levels of follicle stimulating hormone and lutenizing hormone. This study showed no association between occupational exposure to epichlorohydrin and reduced sperm counts. Hormone levels were also comparable with controls.

Venable et al. (1980) conducted a similar study on workers exposed to epichlorohydrin and other chemicals in the production of glycerine. Sperm counts, hormone levels, reproductive history and percent abnormal sperm were determined for 64 epichlorohydrin exposed workers and 63 nonexposed employees. Comparisons were made between exposed and control groups and attempts were made to correlate abnormal findings with the level of epichlorohydrin exposure. No effects on fertility or sperm morphology could be attributed to occupational exposure to epichlorohydrin.

5.5. CHRONIC TOXICITY

Limited information is available regarding the effects of chronic epichlorohydrin exposure in animals. The only chronic study available is that conducted by Laskin et al. (1980), in which male Sprague-Dawley rats were exposed by inhalation. Groups of 100 rats each were exposed at 0, 10, or 30 ppm epichlorohydrin for 6 hours/day, 5 days/week for their lifetimes. A group of 50 rats was untreated and maintained for comparisons. Decreased weight gain was noted in rats treated at 30 ppm after ~40 weeks. Pulmonary congestion, nasal inflammation and pneumonia in all groups (control and treated) caused increased early mortality. The major effect attributed to epichlorohydrin exposure was renal damage with tubular degeneration and occasional glomerular degeneration and hyaline casts. Renal lesions were most severe in the high dose group, but rats treated at 10 ppm also showed a

dose related increased incidence. Renal lesions occurred in 65, 37, 24 and 14% of rats treated at 30, 10, 0 ppm and untreated controls, respectively.

Kremneva and Tolgskaya (1961) reported respiratory effects (bronchitis, bronchial necrosis, thickened alveolar septa and pulmonary edema), renal convoluted tubule necrosis, hepatic fatty degeneration and myocardial changes among rats exposed to epichlorohydrin by inhalation at 170-250 mg/m³ (3 hours/day, 5 days/week) for 5 months. Less severe effects were noted in rats exposed at 20-60 mg/m³ (3 hours/day, 5 days/week) for 6.5 months. Fomin (1966) reported renal damage (necrosis of the convoluted tubules), pulmonary effects (emphysema, desquamation, edema and vascular degeneration), hematological effects, myocardial hemorrhage and CNS damage in rats inhaling epichlorohydrin at 20 mg/m³, continuously for 98 days. Exposure at 2 or 0.2 mg/m³ continuously for 98 days resulted in no histopathological changes.

The effects of inhalation exposure to epichlorohydrin were studied by Quast et al. (1979a) using Sprague-Dawley rats, Fischer 344 rats and B6C3F1 mice. Groups of 20 animals of each sex and strain were exposed at 0, 5, 25 and 50 ppm (0, 19, 95 and 190 mg/m³) epichlorohydrin for 6 hours/day, 5 days/week for 12-13 weeks (61 or 62 exposures). Interim kills of one-half the animals in each group were made after 30 days of exposure and final kills were made at 90 days. Complete clinical and histopathological examinations were conducted. Exposure at 5 ppm for 90 days did not result in any detectable effects in rats or mice. Slight decreased body weight gain was reported in female F344 rats exposed at 25 ppm and in male rats of both strains and in mice of both sexes exposed at 50 ppm. Inhalation exposure to epichlorohydrin most severely affected the nasal epithelia, causing inflammation and degenerative changes in animals of both species after exposure at

25 and 50 ppm for 90 days. The severity of the nasal effects was dose related. Male rats were more sensitive than female rats, Sprague-Dawley rats were more sensitive than F344 rats and mice of both sexes responded similarly but were less sensitive than either strain of rats. Renal and hepatic changes were also evident in rats exposed to 50 ppm epichlorohydrin but not in rats exposed at 25 ppm or mice exposed at any level. Renal lesions consisted of focal tubular nephrosis, dilated tubules and renal cortical swelling. Liver changes consisted of gross pale discoloration and decreased glycogen content.

Lawrence et al. (1972) studied the toxic effects of epichlorohydrin on male Sprague-Dawley rats treated by intraperitoneal injection. Three groups of 12 young rats each were injected with 0.0095, 0.0190 or 0.04774 mℓ epichlorohydrin/kg, 3 days/week for 12 weeks. A vehicle (cottonseed oil) control group was included for comparison. Food consumption was slightly reduced in the two higher dose groups and body weight gain of the highest dose group was reduced compared with controls. Hematological changes (hemoglobin content, hematocrit and erythrocyte counts) showed a dose related decrease, with hemoglobin significantly ($p<0.05$) reduced at all dose levels. Significant increases in organ-to-body weight ratios were noted for the heart, kidneys, liver and brain of rats given 0.04774 mℓ epichlorohydrin/kg for 12 weeks. No histopathological changes of any organs were reported.

In summary, longer term exposure studies of epichlorohydrin have consistently shown effects on the nasal and respiratory system (following inhalation), blood, kidney, liver and brain. NOELs tend to be <5 ppm with histological changes occurring after inhalation exposure at 10-50 ppm.

In humans, the effects of long-term exposure to epichlorohydrin in the workplace among groups of chemical company employees have been studied by several researchers. A retrospective morbidity study of Dow Chemical Company workers was reported to NIOSH (1976) by Kilian (1976). A cohort of 507 employees exposed to epichlorohydrin for ≥6 months to 16 years was identified (most employees had ≤5 years). Employees were classified by job title as having minimal (n=397) or moderate (n=110) exposure but exposure levels were not determined. A high level of respiratory tract illness occurred among the cohort. A medical examination of the workers revealed no apparent effects on blood chemistry or kidney and liver function. The group of workers expected to have the highest exposure to epichlorohydrin did, however, show slightly elevated white blood cell counts and wide fluctuations in monocyte counts.

Sram et al. (1980) conducted hematological examinations on a group of 28 workers exposed to epichlorohydrin for 4 years. Decreased hemoglobin levels were reported in 16 workers while 5 workers each had below normal erythrocyte and leukocyte counts. NIOSH (1976) reviewed a Dow Chemical study that reported below normal leukocyte counts in 39 of 48 workers. Monocyte counts were above normal for 35 of 48 workers, with both blood changes common to 32 of the workers.

Pet'ko et al. (1966) conducted medical examinations of 82 workers employed in the production of epichlorohydrin from dichlorohydric glycerin and studied their health histories for time off that was due to illness. The cohort consisted of 49 men and 33 women (most were age 20-35) Mean epichlorohydrin exposure levels were not reported but isolated exposure levels were 19-21 mg/m³ (4.9-5.5 ppm) and occasional emergency levels reached 210-211 mg/m³ (~54-55 ppm). Based on examination of the ocular mucous membranes,

skin, blood cell morphology, blood bilirubin, cholesterol, and protein content, respiratory organs and function, cardiosvascular system, nervous system and general urinalysis, Pet'ko et al. (1966) concluded that no effect on health could be attributed to epichlorohydrin exposure.

5.6. OTHER RELEVANT INFORMATION

The acute toxic effects of epichlorohydrin following exposure by several routes have been well established in animals (U.S. EPA, 1984a). Levels causing ~50% mortality in rats or mice inhaling epichlorohydrin ranged from ~250-650 ppm for 4-8 hours of exposure (U.S. EPA, 1984a). Death resulted from acute respiratory tract irritation, hemorrhage and severe edema following inhalation of epichlorohydrin (Laskin et al., 1980). At high levels of epichlorohydrin, animals exhibited CNS depression with paralysis of respiration and cardiac arrest, causing death. Quast et al. (1979b) exposed two strains of rats (Sprague-Dawley and F344) and B6C3F1 mice to epichlorohydrin by inhalation at 100 ppm (7 hours/day) for 9 exposures in 12 days. Histopathological examination revealed exposure related effects in the nasal turbinates (squamous metaplasia, hyperplasia, degeneration and inflammation) in all exposed rats and mice. Rats showed renal degeneration and males had slight changes in the epididymides. Mice appeared to be more resistant to the sublethal level of epichlorohydrin (100 ppm) than were rats. Buckley et al. (1984) reported a EC_{50} of 687 ppm epichlorohydrin in exposed rats for reduced breathing (inhalation 6 hours/day, 5 days) and associated nasal and lower respiratory tract lesions.

Epichlorohydrin administered orally to rats and mice causes depression of the nervous system, hyperemia and hemorrhage of organs; subcutaneously, renal damage and hepatic toxicity occur (Kremneva, 1960; Kremneva and Tolgskaya, 1961). The oral LD_{50} values for rats and mice were between 236

and 325 mg/kg (U.S. EPA, 1984a). Death may result from depressed respiration and cardiac arrest or hemorrhage in the lungs and other organs.

Following subcutaneous or intraperitoneal injection, acute LD_{50} values ranged from 113-170 mg/kg in rats, mice, rabbits and guinea pigs (Lawrence et al., 1972; Pallade et al., 1967). Pallade et al. (1967) conducted histopathological examinations of the heart, lungs, kidneys, liver adrenals, spleen, stomach, intestine and brain of rats injected subcutaneously (at 150 and 180 mg/kg) and found the kidney to be the most severely affected. Renal damage included cortical ischemia, medullary congestion, interstitial edema and degeneration and necrosis of convoluted tubules. Surviving rats showed signs of regeneration after day 5 of treatment. The lungs were congested and inflamed, with bronchial desquamation and edema. Other organs generally appeared normal with slight congestion in the heart, stomach, intestinal mucosa and liver of a few animals (Pallade et al., 1967).

Dermal application studies of epichlorohydrin have shown the compound to absorb readily causing systemic toxicity as well as skin irritation and sensitization (U.S. EPA, 1984a). Dermal LD_{50} values ranged from 750-1200 mg/kg for 24-hour exposures in rabbits (Lawrence et al., 1972; Smyth et al., 1962). Toxic signs were similar to those described for inhalation or oral exposure to epichlorohydrin. Respiration was depressed and dead animals showed congestion and edema of major internal organs, renal necrosis and brain hemorrhages. Skin irritation has been reported following application of 0.01 mℓ epichlorohydrin to the clipped abdominal skin of albino rabbits (Smyth and Carpenter, 1948). Epichlorohydrin has been shown to cause sensitization reactions in guinea pigs in one study (Thorgeirrson and Fregert, 1977) while other studies (Lawrence et al., 1972; Weil et al., 1963) reported no sensitization.

In humans, acute exposure to epichlorohydrin in the workplace has caused irritation to the eyes, respiratory tract and skin of workers. At sufficient doses, absorbed epichlorohydrin can cause systemic toxicity (nausea, vomitting, cough, labored breathing and chemical pneumonitis (NIOSH, 1976; U.S. EPA, 1984a). NIOSH (1976) summarized effects on humans and reported that epichlorohydrin at 20 ppm causes transient irritation of the eyes and nose, while at 40 ppm, irritation to the eyes and nose persisted for 48 hours. NIOSH (1976) also reported that levels >100 ppm were intolerable and may cause pulmonary edema and renal lesions. Dermal contact with epichlorohydrin has caused irritation (redness, swelling, itching) and more severe chemical burns (blisters and desquamation) (NIOSH, 1976).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethality of epichlorohydrin has been determined in several species of freshwater fish, daphnids, and one species of marine fish. In the bluegill sunfish, Lepomis macrochirus, mortality was monitored during 96-hour exposures of epichlorohydrin at 10-56 mg/ℓ. The "best-fit" 96-hour LC_{50} value was 35.0 mg/ℓ (Dawson et al., 1977). Mayes et al. (1983) reported 96-hour LC_{50} values of 12.7, 10.6, and 13.2 mg/ℓ for fry, juvenile and subadult fathead minnows, Pimephales promelas, respectively. A 24-hour LC_{50} value of 23 mg epichlorohydrin/ℓ was reported in the goldfish, Carassius auratus (Bridie et al., 1979b). Alabaster (1969) reported 24- and 48-hour LC_{50} values of 72 and 36 mg epichlorohydrin/ℓ, respectively, for the harlequin fish, Rasbora heteromorpha, and estimated a no-effect threshold level of 18 mg/ℓ. Juhnke and Luedemann (1978) reported LC_0, LC_{50} and LC_{100} values of 12, 24, and 35 mg epichlorohydrin/ℓ, respectively, in the golden orfe, Leuciscus idus melanotus, following 48-hour exposures.

The lethal effects of epichlorohydrin following acute exposures were determined in the marine fish, tidewater silversides, Menidia beryllina (Dawson et al., 1977). Fish were exposed at 10, 18 and 32 mg/ℓ for up to 96 hours. Mortality was 100% by 72 hours of exposure at the highest concentration and was 50 and 10%, respectively, after 96 hours at the median and low dose. The best-fit 96 hour LC_{50} value was concluded to be 18 mg epichlorohydrin/ℓ.

The acute toxicity of epichlorohydrin has been studied using the freshwater crustacean, Daphnia magna (Bringmann and Kuehn, 1977, 1982). The 24-hour LC_0, LC_{50} and LC_{100} values in D. magna were 20, 30 and 44

mg/ℓ, respectively, in one study (Bringmann and Kuehn, 1977) and 30, 40, and 53 mg/ℓ, respectively, in the later report.

Studies by Bringmann and Kuehn (1980) tested the toxicity of epichlorohydrin in protozoa, Entosiphon sulcatum, and bacteria, Pseudomonas putida, by determining the toxicant concentration that caused the first detectable decrease in cell multiplication. The toxicity thresholds were 55 and 35 mg/ℓ in the protozoan and bacteria after 72 and 16 hours, respectively.

6.2. CHRONIC EFFECTS

Pertinent data regarding the toxic effects of chronic exposure to epichlorohydrin on aquatic organisms were not located in the available literature cited in the Appendix.

6.3. PLANT EFFECTS

The toxicity threshold values causing the first detectable decrease in cell multiplication in the blue-green alga, Microcystis aeruginosa, and green alga, Scenedesmus quadricouda, were 6.0 and 5.4 mg/ℓ, respectively (Bringmann and Kuehn, 1978; Bringmann, 1975).

6.4. RESIDUE

Pertinent data regarding residues of epichlorohydrin in the aquatic environment or aquatic organisms were not located in the available literature cited in the Appendix. Because of the volatile and reactive nature of epichlorohydrin, however, its long-term persistence in the aquatic environment is not likely.

6.5. OTHER RELEVANT INFORMATION

Additional data relevant to the toxicity of epichlorohydrin on aquatic organisms were not located in the available literature cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The current Occupational Safety and Health Administration (OSHA, 1981) standard for a TWA 8-hour exposure in the workplace is 5 ppm (19 mg/m³). NIOSH (1976) suggested, based on a review of human toxicity data, that the standard be reduced to 0.5 ppm (2 mg/m³) for up to a 10-hour workday and 40-hour workweek with a 15-minute ceiling of 5 ppm (19 mg/m³). OSHA (1981) has not adopted this lower TWA as a standard. The American Conference of Governmental Industrial Hygienists (ACGIH, 1984) has adopted a TWA value of 2 ppm (10 mg/m³) and a STEL of 5 ppm (20 mg/m³). ACGIH (1984) also noted that exposure by dermal contact and cutaneous absorption may significantly contribute to the overall exposure.

The U.S. EPA (1984a) reviewed the FDA regulations that permit the use of epichlorohydrin in resins reacted with ammonia for ion-exchange-treatment of food and potable water. Epichlorohydrin cross-linked resins used for molecular sieves in the processing of foods and whey are also permitted. Starch products may be cross-linked by epichlorohydrin but cannot exceed 0.3%. Epichlorohydrin-based resins used in the manufacture of paper products and adhesives intended for food-related use are permitted.

7.2. AQUATIC

The Clean Water Act prohibits the discharge of >1000 pounds of epichlorohydrin into navigated water since such may be harmful to the aquatic environment (U.S. EPA, 1984a).

8. RISK ASSESSMENT

The available data regarding the carcinogenicity of epichlorohydrin to humans and animals are sufficient to regard the compound as a potential carcinogen. According to the International Agency of Research on Cancer (IARC, 1982) classification of chemicals by weight of evidence for carcinogenicity, epichlorohydrin would be a group 2B compound. This classification reflects positive animal carcinogenicity and probable human carcinogenicity, as well, although sufficient human data are lacking. The detected chromosomal abnormalities in peripheral lymphocytes from epichlorohydrin exposed workers and the induced chromosomal changes in cultured human lymphocytes and mammalian bone marrow cells support the assumption that epichlorohydrin is a probable human carcinogen. Based on the available positive carcinogenicity data, a q_1^* for carcinogenicity will be determined for epichlorohydrin. Assuming there is no threshold dose for carcinogenic effects, it is inappropriate to calculate an ADI level for epichlorohydrin.

The basis for calculating a q_1^* for carcinogenicity of epichlorohydrin could be from epidemiological data in humans (Enterline, 1977, 1980, 1981, 1982), an inhalation study in rats (Laskin et al., 1980), or two oral administration bioassays (Konishi et al., 1980; van Esch, 1982). The U.S. EPA Carcinogen Assessment Group (U.S. EPA, 1984a) has estimated the upper 95% limit of risk from the epidemiological data on Shell Oil Company employees, the inhalation study in rats (Laskin et al., 1980) and the oral carcinogenicity study by Konishi et al. (1980). The study by van Esch (1982) provides the best carcinogenesis data with a dose-related increase in forestomach carcinomas (see Table 5-4) but was not used for quantitative risk estimation for the following reasons: the report was not published or critiqued by the scientific community; the diet administered for the first 56 weeks caused

high level, early mortality and "hairballs" in the stomach. The appearance of hairballs in the stomach may have significantly increased the susceptability to tumor formation by epichlorohydrin in this organ. CAG (U.S. EPA, 1984a) also felt that administration of epichlorohydrin by gavage was not as appropriate a route as administration in drinking water or by inhalation in extrapolating human cancer risk from animal data.

The drinking water study (Konishi et al., 1980), although somewhat short in duration (81 weeks) compared with ideal bioassays and lacking large numbers of animals per dose group (18 per group tested), was used for the derivation of one q_1^* for carcinogenesis. The combined incidence of both papillomas and carcinomas of the forestomach were used for dose-response calculation. The combined tumor response of papillomas and carcinomas in rats killed at 81 weeks was 0/10, 0/9, 2/10 and 9/12 for the control, 375, 750 and 1500 ppm dose groups, respectively (see Table 5-3). Adjusting the treatment levels for noncontinuous exposure, dose levels were 0, 352, 731 and 1,398 ppm, respectively (U.S. EPA, 1984a). Adjusting for the difference in the ratio of water ingested-to-body weight between rats and humans, equivalent treatment levels would be 950, 1974, and 3775 ppm for humans. Assuming a daily water consumption of 2 ℓ/day for a 70 kg adult, the equivalent human dosages are 1.9, 3.9 and 7.6 g or 27.1, 55.7 and 108.6 mg/kg/day. Using the adjusted human dosages and the above incidence of forestomach papillomas and carcinomas in the linearized multistage model, the upper limit maximum q_1^* was 4.7×10^{-3} $(mg/kg/day)^{-1}$. An adjustment for the 81-week experiment compared with lifetime exposure [(104 weeks/81 weeks)^3=2.1] resulted in a final q_1^* of 9.9×10^{-3} $(mg/kg/day)^{-1}$. The upper limit unit risk for 1 µg epichlorohydrin/ℓ in water was 2.8×10^{-7} (U.S. EPA, 1984a).

In comparison, a q_1^* value of 4.8×10^{-3} $(ppm)^{-1}$ and a unit risk level for 1 $\mu g/m^3$ of 1.2×10^{-6} were determined based on data from the inhalation study in rats (Laskin et al., 1980) (see Table 5-2). This risk estimate was determined using the long-term, low-dose exposures (10 and 30 ppm, 6 hours/day, 5 days/week for lifetime) and the nonsignificant incidence (1/100) of nasal squamous cell carcinoma in the 30 ppm group (U.S. EPA, 1984a). Partial lifetime, higher level exposures such as 100 ppm (6 hours/day) for 30 days followed by lifetime observation, and the resulting incidence of nasal squamous cell carcinoma (15/140) was also used for carcinogenesis risk estimation. The resultant lifetime risk estimate was 4.6×10^{-2} $(ppm)^{-1}$ or 1.2×10^{-5} $(\mu g/m^3)^{-1}$, almost 10-fold greater than that for low level long-term exposure. This risk estimate was not acceptable to CAG (U.S. EPA, 1984a) since short-term, high level exposures do not adequately test the carcinogenicity of low doses of epichlorohydrin and do not account for possible changes in effect throughout the lifetime.

The U.S. EPA (1984a) has calculated a risk estimate based on the data for respiratory tract cancer among Shell Oil Company epichlorohydrin workers (Enterline, 1981). A total of 10 cases of lung cancer (2 cases may have resulted from isopropyl alcohol production) occurred while 8.7 were expected (nonsignificant). Excluding the two cancer cases attributed to isopropyl alcohol production, eight cases were observed and 6.53 were expected (nonsignificant difference). Assuming an average exposure level of 5 ppm and exposure duration of 13.4 years, the adjusted lifetime exposure level was 0.29 ppm epichlorohydrin (U.S. EPA, 1984a). A q_1^* of 0.15 $(ppm)^{-1}$ was determined based on 8 observed cases of lung cancer versus 6.53 expected cases.

In conclusion, CAG (U.S. EPA, 1984a) reported the unit risk of 2.8×10^{-7} $(\mu g/\ell)^{-1}$ of epichlorohydrin for lifetime exposure by ingestion of contaminated drinking water (Konishi et al., 1980). For lifetime inhalation exposure, the risk estimate of 4.8×10^{-3} $(ppm)^{-1}$ was reported for long-term low exposures and 4.6×10^{-2} $(ppm)^{-1}$ for conditions of short-term high level exposure (Table 8-1). Although the risk estimate based on human data was 0.15 $(ppm)^{-1}$, these data were used only to support the carcinogenic effect in rats since the increased incidence of lung cancer in humans was not statistically significant.

TABLE 8-1

Summary of Risk Estimates for Epichlorohydrin[a]

Risk estimate (q_1^*)	Unit risk	Comments	Reference
9.9×10^{-3} $(mg/kg/day)^{-1}$	2.8×10^{-7}[b]	For exposure by drinking water	Konishi et al., 1980
4.8×10^{-3} $(ppm)^{-1}$[c]	1.2×10^{-6}[d]	For lifetime inhalation exposure	Laskin et al., 1980
4.6×10^{-2} $(ppm)^{-1}$[c]	1.2×10^{-5}[d]	For short-term, high level inhalation exposure	Laskin et al., 1980

[a]Estimates determined by CAG (U.S. EPA, 1984a)

[b]Upper limit unit risk corresponding to 1 µg/ℓ epichlorohydrin in drinking water

[c]The experimental concentration was considered equivalent to human exposure concentrations so that no species-to-species weight corrections were made.

[d]Upper limit unit risk corresponding to 1 $\mu g/m^3$ epichlorohydrin in air

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Data adequate for the derivation of a chronic toxicity RQ are limited to one chronic inhalation study (Laskin et al., 1980) and several subchronic inhalation studies (see Section 5.5.). No oral administration studies of adequate duration were available. CSs and RQ values for epichlorohydrin have been previously reported (U.S. EPA, 1983).

The most appropriate data for derivation of an RQ are those reported by Laskin et al. (1980). Groups of 100 rats were exposed at 0, 10 or 30 ppm epichlorohydrin (6 hours/day, 5 days/week) for their lifetimes. Renal damage (tubular and glomerular degeneration with hyaline casts) occurred in 24, 37 and 65% of the rats in the respective dose groups and severity was dose related. The human MED was 51.7 and 155.3 mg/day for exposure at 10 and 30 ppm (37.8 and 113.5 mg/m^3), respectively (Table 9-1). The human MED values correspond to the RV_d of 2.9 and 2.2, respectively. The RV_e of 7 was used since renal lesions included atrophy and degenerative changes of tubular and glomerular epithelia. The CS, a product of the RV_d and RV_e, is 21 for the low-dose group and 15.5 for the high-dose group. The CS results in an RQ of 100.

Comparatively, CS and RQ values can be determined from the subchronic studies by Quast et al. (1979a) and Fomin (1966) (Table 9-1). Quast et al. (1979a) reported degeneration of the nasal epithelia with hyperplasia and metaplasia in rats exposed at 25 and 50 ppm (94.6 and 189.2 mg/m^3; 6 hours/day, 5 days/week) for 90 days. Tubular nephrosis also occurred in rats treated at the high-dose level. The human MED values were determined by applying an uncertainty factor of 10 to the subchronic effective dose to approximate a chronic effect level. The MED values are shown in Table 9-1.

TABLE 9-1

Composite Scores for the Chronic Inhalation Toxicity of Epichlorohydrin

Species	Animal Exposure	Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Rats	37.8 mg/m³, 6 hours/day, 5 days/week	51.7	2.9	37% developed renal damage (predominantly degenerative tubular changes) vs. 24% of sham controls and 14% of untreated controls	7	20.5	100	Laskin et al., 1980
Rats	113.5 mg/m³, 6 hours/day, 5 days/week	155.3	2.2	65% developed renal damage (predominantly degenerative tubular changes) vs. 24% of sham controls and 14% of untreated controls; low incidence of nasal cavity tumors and squamous metaplasia	7	15.5	1000	Laskin et al., 1980
Rats	94.6 mg/m³, 6 hours/day, 5 days/week	12.9	3.8	Inflammatory and degenerative changes in the nasal turbinates (rhinitis, focal erosions, hyperplasia, and metaplasia with a squamous appearance)	7	26.8	100	Quast et al., 1979a,b
Mice		11.8	3.9		7	27.2	100	
Rats	189.2 mg/m³, 6 hours/day, 5 days/week	25.9	3.4	Inflammatory and degenerative changes in the nasal turbinates (rhinitis, focal erosions, hyperplasia, and metaplasia with a squamous appearance); focal tubular nephrosis in rats; gross pathological changes in liver in half of male rats; altered epididymal contents in several male rats; slight weight loss	7	23.7	100	Quast et al., 1979a
Mice		23.7	3.4		7	23.8	100	
Rats	19.7 mg/m³ 24 hours/day	15.1	3.7	Decrease in blood nucleic acids; increase in urinary coproporphyrin; reduced weight gain; prolonged latent periods in a motor defense reaction test; abnormalities of the lungs; cloudy swellings of the epithelium of the convoluted tubules; interstitial hemorrhage and venous congestion of the heart; severe lesions of brain neurons.	6	22.4	100	Fomin, 1966

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Based on the severity of nasal effects, an RV_e of 7 was used for both dose levels. The resulting CS values correspond to an RQ of 100. The CS values determined from these data (Quast et al., 1979a) corroborate the CS values determined from the chronic study (Laskin et al., 1980). Similarly, data reported by Fomin (1966) can be used to determine a CS and RQ. Rats exposed at 5.2 ppm (19.7 mg/m³) continuously for 98 days developed cloudy swelling of tubular epithelia in the kidney and neuronal lesions of the brain (no apparent impairment of function). Applying an uncertainty factor of 10 to the subchronic experimental dose for chronic exposure, a human MED of 15.1 was determined. The RV_d was 3.7. Based on the reported effects, an RV_e of 6 was deemed appropriate. The CS and RQ were 22.4 and 100, respectively. The CS of 22 supports the values derived from chronic exposure data (Laskin et al., 1980) and those from the subchronic study of Quast et al. (1979a).

The CS of 20.5 and RQ of 100 is chosen to represent the hazards associated with chronic exposure to epichlorohydrin (Table 9-2; Laskin et al., 1980). Although the values derived from the subchronic studies are slightly more conservative, these values are less reliable measures of the chronic toxicity hazard of epichlorohydrin since they were based upon short-term toxicity tests and an inherent uncertainty factor was applied in the derivation of the RQ.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=^1/ED_{10}$) FOR CARCINOGENICITY

Epichlorohydrin has been adequately shown to be a contact carcinogen in animals, inducing tumors in tissues of primary contact depending on route of exposure. Nasal cavity carcinomas were induced in rats inhaling epichloro-

TABLE 9-2

Epichlorohydrin

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose*:	0.0, 51.7, 155.3 mg/day
Effect:	Renal lesions (primarily tubular degeneration) 24, 37, and 65%, respectively
Reference:	Laskin et al., 1980
RV_d:	2.9, 2.2
RV_e:	7, 7
Composite Score:	20.5, 15.5
RQ:	100

*Equivalent Human Dose

hydrin (Laskin et al., 1980). Forestomach papillomas and carcinomas developed in rats ingesting epichlorohydrin orally (Konishi et al., 1980; van Esch, 1982). Epichlorohydrin has also produced local sarcomas following subcutaneous injection (Van Duuren et al., 1974). Additional evidence in support of the classification of epichlorohydrin as a carcinogen is that of Enterline (1981), which suggests an increase in lung cancers among epichlorohydrin workers (no significant increase in cancer cases) and the numerous positive mutagenicity assays (see Section 5.2.). Based on the IARC classification scheme for ranking chemicals based on carcinogenicity, epichlorohydrin would be a group 2B chemical (IARC, 1982).

The potency factor (F-factor) for epichlorohydrin could be derived from the data reported by Laskin et al. (1980) (see Table 5-2), van Esch (1982) (see Table 5-4) or Konishi et al. (1980) (see Table 5-3). Laskin et al. (1980) reported that 15 of 140 rats treated for 30 days with 100 ppm epichlorohydrin by inhalation developed nasal squamous-cell carcinoma when observed for their lifetime. Since exposure to epichlorohydrin was for only 30 days at a relatively high level, these data do not adequately estimate the long-term, low level carcinogenic potential of epichlorohydrin (U.S. EPA, 1984a). Since epichlorohydrin was administered for a short interval, calculating a potency factor would result in a spuriously high value since the absorbed dose is expanded over the lifetime of the organism.

Incidence data for the development of forestomach carcinomas and papillomas following gavage treatment with epichlorohydrin in rats (van Esch, 1982) could also be used for the derivation of a potency factor. This study, however, has been regarded by CAG (U.S. EPA, 1984a) as inappropriate for determining the carcinogenic potential of epichlorohydrin for several

reasons: (1) the study has not been published; (2) the formation of "hair-balls" (trichobezoars) in the stomach due to a high-fiber diet may have promoted tumor formation by epichlorohydrin; (3) exposure by gavage was not as appropriate an exposure route for epichlorohydrin as exposure through the drinking water.

The data reported by Konishi et al. (1980) was selected as the most appropriate for ranking the carcinogenic potency of epichlorohydrin. Groups of male rats were treated with epichlorohydrin in the drinking water at 0, 375, 750, and 1500 ppm for 81 weeks. The total ingested doses of 0, 5.0, 8.9, and 15.1 g epichlorohydrin/rat, respectively, were reported for each group. Transformed doses were 0, 25.2, 44.8 and 76.1 mg/kg/day, respectively (Table 9-3). The combined incidence of forestomach squamous-cell carcinomas and papillomas was 0/10, 0/9, 2/10 and 9/12 for each group, respectively. The F-factor based on these data was 0.03 (Table 9-3), which places epichlorohydrin in the low potency group according to the CERCLA (Comprehensive Environmental Response, Compensation and Liability Act) ranking scheme (U.S. EPA, 1984c). This is consistent with the conclusion that epichlorohydrin is among the weakest of classified carcinogens based on relative potency (U.S. EPA, 1984a).

TABLE 9-3

Derivation of Potency Factor (F)

Agent: Epichlorohydrin

Reference:	Konishi et al., 1980			
Exposure route:	oral			
Species:	rat			
Strain:	Wistar			
Sex:	male			
Vehicle or physical state:	drinking water			
Body weight[a]:	0.35 kg			
Duration of treatment:	567 days			
Duration of study:	567 days			
Lifespan of animal[a]:	730 days			
Target organ:	forestomach			
Tumor type:	squamous-cell carcinoma and papillomas combined			
Experimental doses/exposure:	1500 ppm (15.1 g/rat)[b]	750 ppm (8.9 g/rat)[b]	375 ppm (5.0 g/rat)[b]	0.0 ppm (0.0 g)[b]
Transformed doses (mg/kg/day):	76.1	44.8	25.2	0.0
Tumor incidence:	9/12	2/10	0/9	0/10
$1/ED_{10}$ (F Factor):	0.03			

[a] estimated

[b] reported

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in November, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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Grayson, M. and D. Eckroth, Ed. 1978-83. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

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ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. United States Dept. Interior, Fish and Wildlife Service. Resource Publ. 137. Washington, DC.

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Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. U.S. EPA, Office Pesticide Programs. Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

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